ACIP Anthrax Vaccine Work Group

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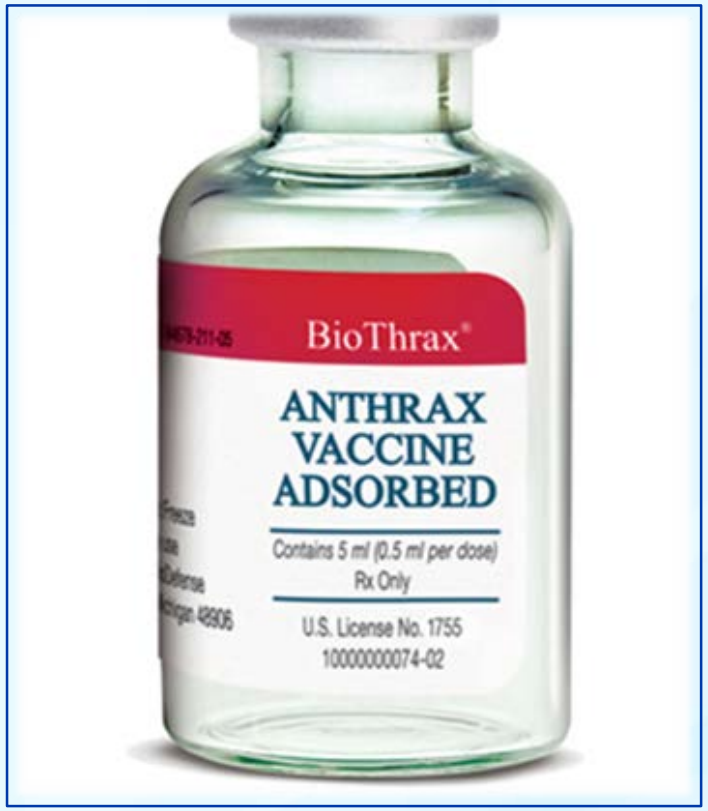
Division of High-Consequence Pathogens and Pathology

Summary of 2010 ACIP Recommendations for Anthrax Vaccine Adsorbed (AVA)



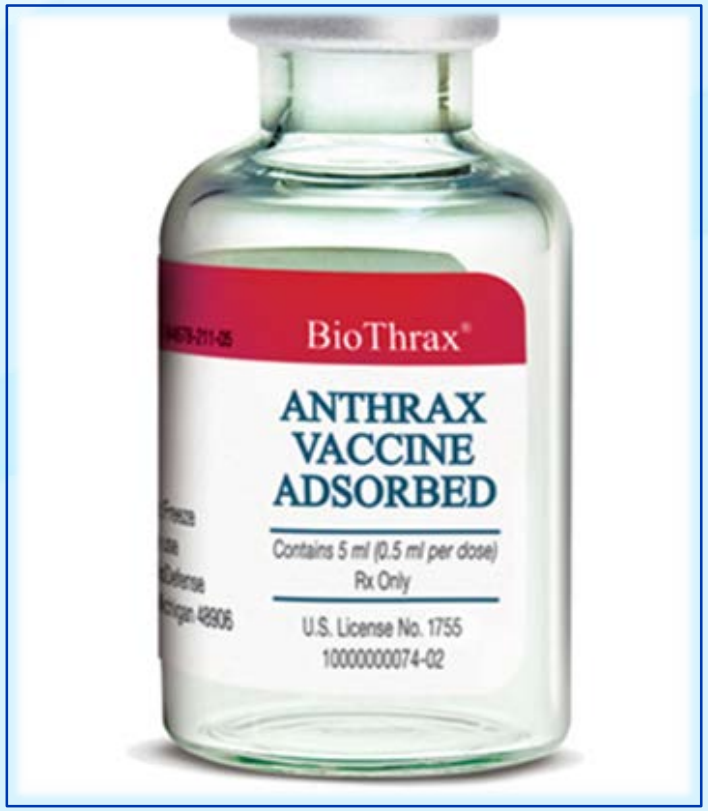
- **Pre-Exposure Prophylaxis (PrEP)**
  - Intramuscular (IM) route
  - 5-dose priming series at 0, 1, 6, 12, and 18 months
  - Then annual booster

- **Post-Exposure Prophylaxis (PEP) under IND/EUA**
  - Subcutaneous (SC) route
  - 3-dose series at 0, 2, and 4 weeks postexposure
  - Co-administration of antibiotics for 60 days

Changes to the Licensed Indications since 2010

- **Pre-Exposure Prophylaxis (PrEP)**
  - Intramuscular (IM) route
  - 3-dose priming series at 0, 1, and 6 months
  - Booster doses at 12 and 18 months, then annually

- **Post-Exposure Prophylaxis (PEP)**
  - Subcutaneous (SC) route
  - 3-dose series at 0, 2, and 4 weeks
  - Co-administration of antibiotics for 60 days



Use of AVA in Special Populations

- AVA is licensed for persons 18 through 65 years of age
- There are little to no data on the use of AVA in special populations.
- Benefit of vaccine outweighs the potential harm of unknown AEs
- Use under an IND or EUA
- Policy changes are for all ages

Recent AVA Safety Studies

Study	Study Design (# Participants)	Measure(s)	Outcome
Phillips CJ. *Vaccine.* 2009	Cohort study (1497)	Develop Squalene Antibodies	No association between squalene antibody status and chronic multi-symptom illness
Sulsky SI. *Vaccine.* 2011	Cohort study (1,001,546)	Disability Risk	AVA not associated with differences in risk of disability
Sulsky SI. *Vaccine.* 2011	Case-control study (154,780)	Disability	No association between receipt of AVA and long-term disability
Stewart B. *Vaccine.* 2012.	Randomized controlled trial (1562)	Health-Related Quality of Life	No association between receipt of AVA and quality of life over a 42-month period
Duderstadt, SK. *Vaccine.* 2012	Retrospective population-based cohort (2.3 million)	Type 1 Diabetes	No increased risk for AVA and type 1 diabetes
Conlin AM. *Vaccine.* 2015	Retrospective cohort (126,839)	Birth Defects	No associations between AVA vaccination during pregnancy and birth defect risk
Bardenheier BH. *Military Medicine.* 2016	Matched case-control (463)	Rheumatoid Arthritis (RA) Systemic Lupus Erythematosus (SLE)	AVA associated with recent onset but not long term RA No association with SLE

AVA Safety

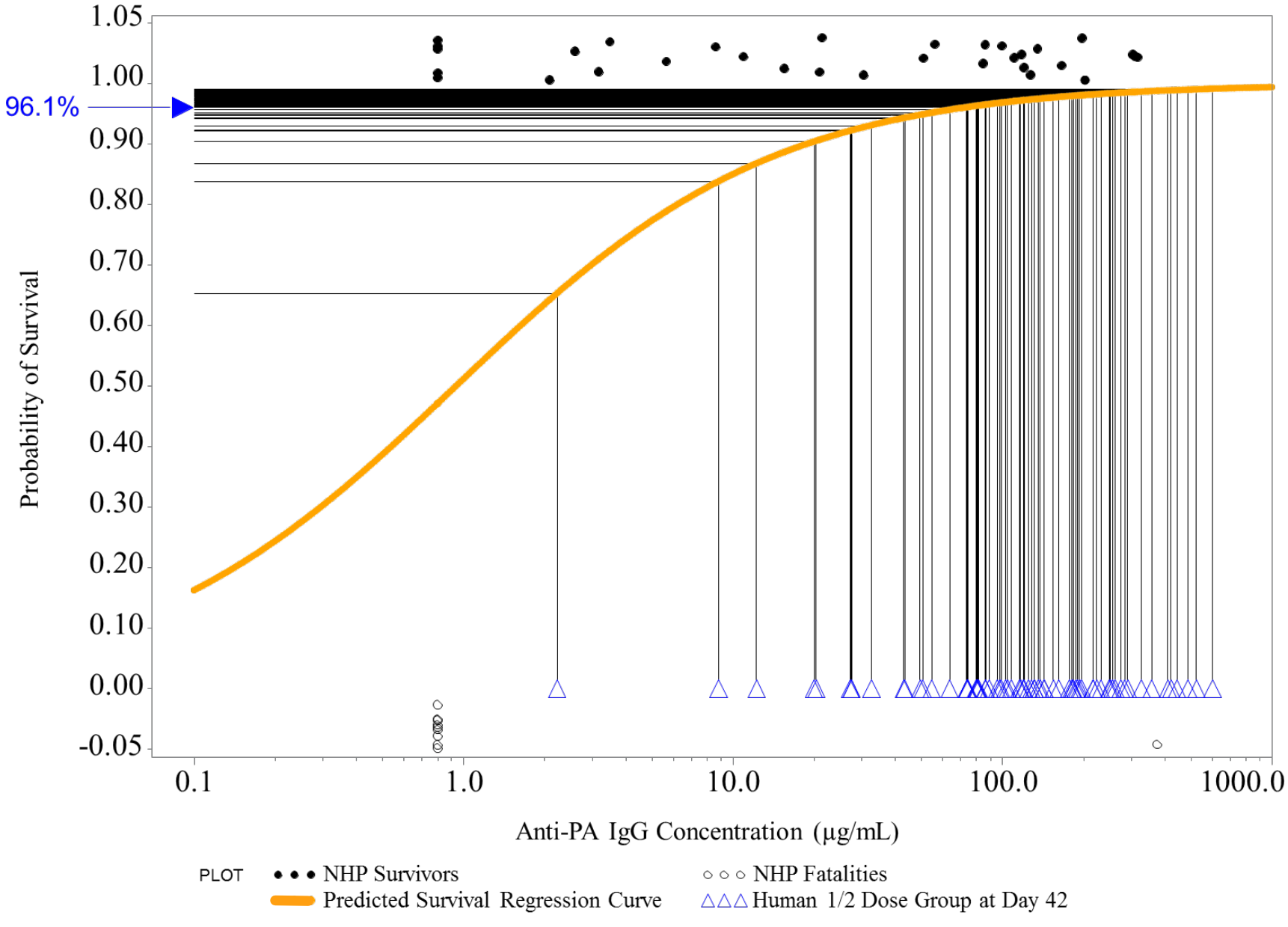
- No new safety concerns since December 2008 based on updated VAERS review and a review of the published literature
- Data support safety of AVA for use as pre-exposure and post exposure prophylaxis given high mortality associated with anthrax
- More data are needed to evaluate safety in pediatric populations

Understanding AVA Effectiveness: Predicting Human Survival Based on "Animal Rule" Data

- Animal survival data (Sivko, 2016)
  - Supporting data (Ionin, 2013 and Quinn, 2012)

- Immune response in humans
  - Subset of a pre-exposure (0, 14 and 28 days, then 6, 12, and 18 months) regimen study used to compare IM vs SC route of administration (Wright, 2014)
  - Dose sparing schedules (Bernstein, 2014)
    - 2 full doses at 0 and 14 days
    - 2 full doses at 0 and 28 days
    - 3 half doses at 0, 14, and 28 days

Predicting Survival Using COP



NHP N = 42

Correlate of Protection Model: Anti-PA IgG Predicted Survival of 0, 14, 28 ½ dose group at day 42 is 96.1%

Summary of Policy Questions for ACIP Consideration

Optimizing use of vaccine during a large mass vaccination event

1) May the intramuscular (IM) route of administration (ROA) be used if the subcutaneous (SC) ROA presents clinical, operational, or logistical challenges that may delay or prevent effective vaccination?
2) Should there be an inadequate supply of anthrax vaccine available for PEP, may either 2 full doses or 3 half doses of AVA be used to expand vaccine coverage?

Use of antimicrobials in conjunction with vaccine

3) In immunocompetent individuals who are being vaccinated with anthrax vaccine, do antimicrobials provide adequate protection when given for:
   a) At least 42 days after the first vaccine dose, or
   b) 2 weeks after the last vaccine dose, whichever comes later

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IM versus SC Route of Administration Considerations - Immunogenicity

Predicting survival for IM vs SC at Days 28 and 56		
	IM	**SC**
Day 28	n = 241 Anti-PA IgG = 30.6 µg/mL* Predicted Survival = 88.6%	n=242 Anti-PA IgG = 52.6 µg/mL* Predicted Survival = 92.4%
Day 56	n = 234 Anti-PA IgG = 87.5 µg/mL Predicted Survival = 95.6%	n = 235 Anti-PA IgG = 100.6 µg/mL Predicted Survival = 96.1%

***Statistically significant difference**

IM versus SC Route of Administration Considerations – Adverse Events

- SC route of administration produced significantly more frequent localized adverse events in most all parameters evaluated.

- There was a higher occurrence of generalized muscle ache amongst IM recipients compared to SC

IM versus SC Route of Administration Considerations – Operational Concerns

- Adherence to antimicrobial PEP wanes over time
  - Higher titers at 30 days would protect more individuals that are not adherent to antimicrobial PEP
- Adherence to vaccine PEP
  - IM administration results in a lower proportion of localized adverse events compared to SC administration
- In a large anthrax event, efficiency of administering vaccine to a large number of people is a major concern

ACIP Work Group Conclusions

- The SC route of administration is preferred over the IM route of administration for PEP due to the higher antibody concentrations achieved at 4 weeks
- Supported IM use when operationally challenging
- During a large-scale emergency response, AVA for PEP may be administered using an IM route if the SC route of administration poses significant materiel, personnel, or clinical challenges that may delay or preclude vaccination
- Individuals that experienced significant adverse events from AVA administered by the SC route of administration may elect to receive the subsequent vaccine dose(s) by the IM route in consultation with a provider

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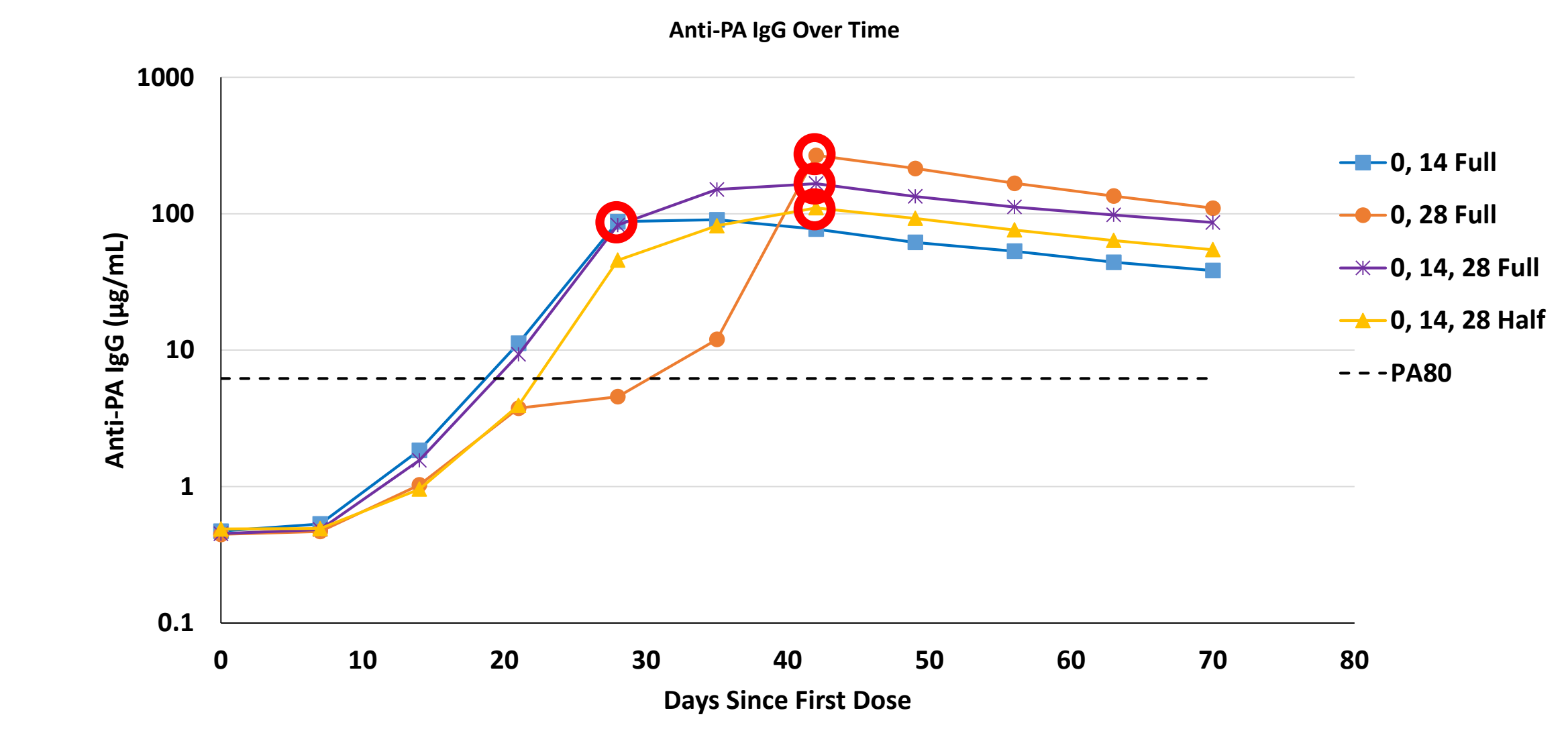
Human Immunogenicity with Dose Sparing Schedules



Bridging Human data to Animal Survival (Correlates of Protection)

Predicted Survival at Days 28, 42, and 63

Day 28

Assay	0, 14 Full	0, 28 Full	0, 14, 28 Full	0, 14, 28 Half
Anti-PA IgG	95.8%	72.6%	95.8%	91.1%
(N)	(79)	(81)	(81)	(79)

Day 42

Assay	0, 14 Full	0, 28 Full	0, 14, 28 Full	0, 14, 28 Half
Anti-PA IgG	95.5%	98.1%	97.4%	96.1%
(N)	(69)	(78)	(79)	(74)

Day 63

Assay	0, 14 Full	0, 28 Full	0, 14, 28 Full	0, 14, 28 Half
Anti-PA IgG	93.3%	97.0%	96.4%	94.2%
(N)	(69)	(77)	(63)	(72)

Work Group Conclusions

- All dose-sparing schedules provided high levels of protection by two week after the last dose.
- The two-full-dose strategy will expand the vaccine supply by 50% and the three-half-dose strategy will expand it by 100%. The choice of dose-sparing schedule depends on anticipated vaccine shortage.
- If number of potentially exposed individuals exceeds vaccine supply, it would be beneficial to protect larger numbers of individuals with slightly lower protective levels

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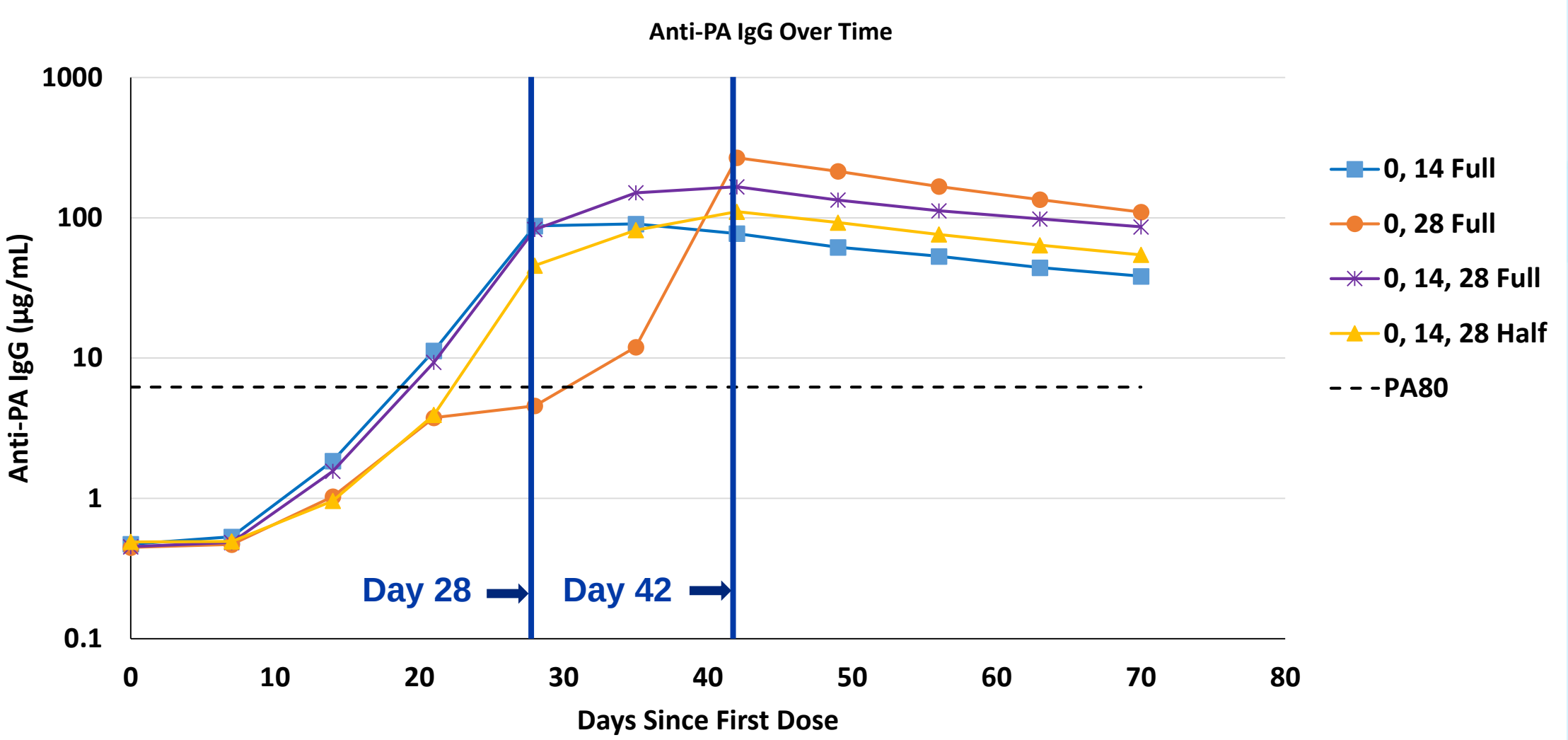
Decrease Duration of Antimicrobial PEP



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Day 42				
Assay	0, 14 Full	0, 28 Full	0, 14, 28 Full	0, 14, 28 Half
Anti-PA IgG	95.5%	98.1%	97.4%	96.1%

Day 63				
Assay	0, 14 Full	0, 28 Full	0, 14, 28 Full	0, 14, 28 Half
Anti-PA IgG	93.3%	97.0%	96.4%	94.2%

❑ **Peak Protection**

Decrease Duration of Antimicrobial PEP

- For most of the dose-sparing schedules as well as the licensed schedule, day 42 is two weeks after the last dose. For the day 0 and 14 dose sparing schedule, day 28 is two weeks after the last dose.
- Peak response for all dosing schedules is 2 weeks after the last dose
- Peak response is highly protective
- Allowing antimicrobial use to stop once peak immune response is reached would shorten antimicrobial requirement and potentially reduce adverse events related to continued antimicrobial use.
- Emphasis on adherence until immune response is sufficient may improve adherence for the shorter duration

Decrease Duration of Antimicrobial PEP

- For immunocompetent individuals, AbxPEP should be given concurrent with VxPEP and AbxPEP should continue for at least 42 days after their first dose or two weeks after their last dose of the vaccine series, whichever comes last.
- Individuals with immunocompromising medical conditions, or on immunosuppressive medication, or in groups in whom immunologic responses to AVA are unknown, should take 60 days of AbxPEP concurrent with vaccine.

Policy Consideration Summary for ACIP Committee

- May the IM ROA be used if the SC ROA presents clinical, operational, or logistical challenges that may delay or prevent effective vaccination?
- Should there be an inadequate supply of anthrax vaccine available for PEP, may either 2 full doses or 3 half doses of AVA be used to expand vaccine coverage?
- In immunocompetent individuals may AbxPEP be discontinued at 42 days after the first vaccine dose or 2 weeks after the last vaccine dose, whichever comes later?
  - If yes, can this be extended to healthy 2 to 17 year olds?

VOTE: Anthrax Vaccine Use for PEP in a Mass Vaccination Campaign

- The IM ROA may be used if the SC ROA presents clinical, operational, or logistical challenges that may delay or prevent effective vaccination
- Should there be an inadequate supply of anthrax vaccine available for PEP, either 2 full doses or 3 half doses of AVA may be used to expand vaccine coverage
- In immunocompetent individuals, antimicrobials given in conjunction with vaccine may be discontinued at 42 days after the first vaccine dose or 2 weeks after the last vaccine dose, whichever comes later